REMARKS

Claim 1 has been amended to correct a typographical error; the claim now recites "N-oxide form**s.**" Claims 5, 10, and 13 have been canceled, without prejudice. The Applicants reserve the right to file the subject matter of the cancelled claims in continuing or divisional application. Claim 7 has been amended to even more particularly describe the recited subject matter. The Office has indicated that claims 1-4, 8, and 9 are allowable.

The undersigned thanks Examiner Leeser for the courtesy of granting the telephonic interview of May 27, 2008. The rejection of claim 7 was discussed, but no agreement was reached.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 7 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabling. The Applicants disagree with the Office's position and request reconsideration and withdrawal of the rejection.

"All questions of enablement are evaluated against the claimed subject matter. . . . Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims." MPEP 2164.08. In the October 11, 2007 Action, the Office incorrectly identified the subject matter of claim 7 as being "drawn to ***compositions*** used to treat . . . depression anxiety, movement disorders, psychosis, Parkinson's disease, and body weight disorders with a [] compound of Formula (I)." Action at 5. This is inaccurate. Claim 7 is directed to ***methods of treatment***, wherein the methods comprise administering a compound of Formula I to an animal in need of treatment of depression, anxiety, movement disorders, psychosis, Parkinson's disease, or body weight disorders.

To satisfy the enablement requirement, the disclosure, when filed, must contain sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. *See* MPEP 2164.01. In addition, "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.,* 857 F.2d 778, 785 (Fed.

Cir. 1988); MPEP 2164.01. Thus, the enablement of claim 7 is established when the disclosure contains sufficient information as to enable one skilled in the art to administer a compound of Formula I to an animal in need of treatment of depression, anxiety, movement disorders, psychosis, Parkinson's disease, or body weight disorders, without undue experimentation. The Applicants assert that the present specification, along with the knowledge of one skilled in the art, provides sufficient information to enable one skilled in the art to (1) make the compounds of Formula I; (2) identify whether an animal is in need of treatment of depression, anxiety, movement disorders, psychosis, Parkinson's disease, or body weight disorders; and (3) administer a compound of Formula I to the animal, without undue experimentation.

In the October 11, 2007 Action, the Office set forth its reasoning why claim 7 is allegedly nonenabled.[1] ***None*** of the reasons set forth by the Office provide any evidence that the quantity of experimentation required to practice claim 7 is undue. Indeed, it appears that in mischaracterizing the scope of claim 7, the Office failed to properly apply the enablement test to the pending claim.

Nevertheless, even if the Office properly determined the scope of claim 7, and the Applicants do not concede that such is the case, the Office merely recites that experimentation is necessary and that it is complex. Yet the pharmaceutical arts ***routinely*** engage in just the kind of experimentation the Office identifies as necessary to practice claim 7. While results in the pharmaceutical arts might not always be predictable, the field has established, routine tests to determine the appropriate pharmacological properties necessary to practice the claimed invention. *See, e.g., Neurotransmitters and Neuromodulators Handbook of Receptors and Biological Effects*, attached herewith. The Applicants assert that

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[1] In that Action, the Office stated that:
The "state of the prior art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art." Action at 5.
"It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. . . . In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of claim 1 would be useful to treat . . . depression, anxiety, movement disorders, psychosis, Parkinson's disease, and body weight disorders." Action at 6.
"The level of skill in the art is high. Due to the unpredictability in the pharmaceutical arts, however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity." Action at 7.

one of skill in the art can practice the claimed invention using the disclosure provided in the application as filed, along with the knowledge of one skilled in the art, without *undue* experimentation. Withdrawal of the rejection is requested.

Rejection based on 35 U.S.C. 112, second paragraph

Claims 5, 10, and 13 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. While the Applicants do not necessarily agree, these claims have been cancelled in order to further the prosecution of the pending application. The Applicants reserve the right to file the subject matter of the canceled claims in continuing or divisional applications. The rejection is moot.

* * *

The Applicants assert that the foregoing constitutes a full and complete response to the May 5, 2008 Non-Final Office Action and that claims 1-4 and 7-9 are in condition for allowance. An early Notice to that effect is, therefore, earnestly solicited.

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The early concept was that all members of the α-2 receptor family were coupled to a pertussis toxin-sensitive inhibitory G protein (G_i). However, it turned out that this is true exclusively for the receptor subtype α-2C. While the receptor α-2B is linked to a pertussis toxin-insensitive G protein and is capable of activating adenylate cyclase, the α-2A receptor inhibits adenylate cyclase at low agonist concentrations and shows a reverse effect at high concentrations. Additionally, it has been shown that activation of α-2A receptors involves the stimulation of the mitogen-activated protein kinase (MAPK).

The α-2 receptor family has been found primarily on presynaptic membranes, whereas the α-1 receptors occur at postsynaptic sites.

Adrenergic β receptors

Two subtypes of β adrenoceptors were originally identified as β1 and β2.

The β1 receptors are expressed primarily in neurons, whereas the β2 receptors are found in glia. In addition, a third member of the β adrenoceptors has been identified which shows only a minor affinity for epinephrine or norepinephrine. This receptor subtype was named "atypical" β adrenoceptor or β3 receptor.

A further difference in the β3 receptor as compared to the other β subtypes is its behavior in the presence of CGP12177. This substance is an antagonist of β1 and β2 receptors, but shows a partial agonistic effect when exposed to β3 receptors.

All three subtypes of β adrenoceptors are coupled to G_s proteins, which leads to a stimulation of adenylate cyclase activity.

A prolonged exposure of the β adrenoceptors to their agonists reduces the responsiveness of the receptors (desensitization). Desensitization includes functional uncoupling from the G proteins and removal of the receptor from the membrane. The functional uncoupling from G proteins may occur as a result of phosphorylation of the intracellular domains of the receptor, either by G protein-coupled receptor kinases (GRKs) or by protein kinases.

3.7.5 Biological Effects

The functional consequences of noradrenergic receptor activation can be either inhibitory or excitory. On the one hand, norepinephrine frequently reveals inhibitory effects. Electrical stimulation of the locus coeruleus or the iontophoretic application of norepinephrine induces a decrease in the spontaneous activity of the neurons. On the other hand, norepinephrine seems to potentiate the neuronal responses to visual, auditory or nociceptive stimuli.

As mentioned earlier, norepinephrine has been found to colocalize with some neuropeptides, like NPY or galanine. Under experimental conditions (by increasing the frequency of electrical stimulation of a sympathetic nerve), NPY and norepinephrine are co-released and act synergistically on vasoconstriction. Furthermore, NPY inhibits the release of norepinephrine.

The activation of adrenoceptors of the α- and β-type exhibits almost inverse phsiological effects. In peripheral tissues, for example, activation of α1 adrenoceptors causes vasoconstriction, enhances glycogenolysis and more generally induces the contraction of smooth muscle cells, whereas activation of β adrenoceptors leads to vasodilatation, bronchodilatation and positive ionotropic and chronotropic effects on heart tissue.

Neuronal activation of β adrenoceptors is responsible for hyperpolarization, which depends on the activation of cAMP, accompanied by an increase in membrane resistance.

A further aspect of functional relevance is the potentiating effect of noradrenaline on some neuromodulators and neurotransmitters. For example, it has been found that norepinephrine increases vasoactive intestinal protein (VIP)-induced effects on glycogenolysis and enhances the neuronal responses to excitatory amino acids, like glutamate, in the cerebral cortex.

With respect to the locus coeruleus and its dominant role in the organization of the intracerebral noradrenergic system, the involvement of this nucleus in the regulation of general attention and circadian rhythm is of interest. However, the predominant physiological function of the central noradrenergic system is its response to stress-induced stimuli.

The induction of stress is coupled to an enhanced activity of the locus coeruleus which, because of its widespread projections into cortical and subcortical structures and lower brain stem areas, affects a variety of physiological functions. Evidently, the locus coeruleus seems to work as a relais for the noradrenergic projection, which is regulated by hypothalamic inputs such as the neuropeptide corticotropin-releasing factor (CRF).

Administration of CRF, for example, causes an increase in the plasmatic concentration of norepinephrine and CRF stimulates the synthesis of tyrosine hydroxylase (the enzyme which is necessary for the biosynthesis of norepinephrine) within the locus coeruleus.

3.7.6
Neurological Disorders and Neurodegenerative Diseases

The locus coeruleus and norepinephrinergic neurons in the reticular nuclei of the substantia nigra (A1 and A2) can be targets of degenerative diseases.

In Parkinson's disease, a massive loss of neurons can be observed in both brain areas, particularly if the disease is coupled with dementia, the loss of neurons in the locus coeruleus being significantly higher than in the reticular nuclei. However, the loss of norepinephrinergic neurons is not restricted to the brain stem, but also includes neurons in the cerebral cortex. Although the dopaminergic system plays the dominant role in Parkinson's disease, norepinephrinergic deficits seem to be responsible for the clinical phenotype of this disease, especially in the manifestation of deficits of cognitive function.

Postmortem studies have consistently shown norepinephrinergic system involvement in Alzheimer's disease with decreased norepinephrine levels. The ma-

jority of studies indicate significantly decreased cortical and subcortical levels of norepinephrine in the frontal medial gyrus, temporal superior gyrus, cingulated gyrus, hippocampus, amygdala, thalamus, hypothalamus, striatum and the LC.

The loss of norepinephrinergic neurons in the LC has been well established in patients with Alzheimer's disease; and it has not been found in other types of dementia, such as vascular dementia. Concurrent with the loss of NE in the LC is an increase of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylgycol (MHPG), indicating a compensatory mechanism for LC norepinephrine loss. There is a well established link between AD severity and loss of noradrenergic neurons. Norpepinephrine levels in the brain of AD patients have also been found to have an inverse relationship with cognitive impairment.

The norepinephrinergic system seems to be indirectly involved in depression. The compound reserpine can provoke depression and a variety of antidepressive agents prolong the half-life of catecholamines, either by inhibition of their reuptake or by decreasing the metabolic rate (for example, by inhibiting monoamine oxidase; MAO). Modifications to the density of epinephrinergic receptors and phasic variability in the level of norepinephrinergic metabolites have been found in patients suffering from depression. In particular, postsynaptic α_2 receptor down-regulation seems to be prevalent in depression, combined with increased presynaptic receptor sensitivity and increased α_2 receptor density in the LC. Decreased norepinephrinergic receptor sensitivity and increased norepinephrinergic turnover have been noted in patients with anxiety, generalized anxiety disorder and posttraumatic stress disorder.

Some experimental data speak in favor of an involvement of norepinephrine in epilepsy, since norepinephrine inhibits the propagation of seizures or diminishes their extent. Also, vagal nerve stimulation (VNS) has served as a versatile tool in treating patients suffering from refractory epilepsy. Norepinephrine has been suggested to be involved in the prophylactic antiseizure effects of VNS. Most of the data on a link between norepinephrine and epilepsy stem from epidemiological studies and pharmacological effects showing that norepinephrinergic and/or serotonergic transmission are both anticonvulsant and antidepressive. However, most of the the data indicating a direct correlation between norepinephrine and epilepsy were obtained from animal models and need to be substantiated for human epilepsy.

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3.8.5 Biological Effects

Because of its receptor diversity and divergence in transduction pathways, serotonin modulates several biological functions in the central nervous system. The serotonin system exhibits sexual dimorphism, since differences in the expression of mRNA and in the binding of serotonin receptors (subtypes 1A and 2A) between sexes have been described by *in situ* hybridization and autoradiography. For instance, mRNA of the 5-HT1A receptor shows distinctly different expression patterns in female and male rats.

Serotonin influences processes related to memory and learning, sexual behavior and feeding behavior. The latter becomes apparent in transgenic mice, which overexpress 5-HT2C receptors. The transgenics reveal a significantly higher body weight than wild types. In addition, the 5-HT2 antagonist ketanserin inhibits salt appetite induced by sodium depletion. Serotonin seems also be involved in regulating agressive behavior. For example, it has been shown that, after a certain period of isolation, 5-HT1B-deficient mice become more aggressive than wild-type littermates. Since these findings are based on animal models, one must be cautious about assuming that they are directly relevant to human beings.

Within the central nervous system, serotonin plays a significant role in nociception. Experimental data obtained by electrical stimulation of the raphe nuclei speak in favor of this assumption, since the electrical stimulus induces powerful analgesia. In addition, the selective destruction of serotonergic cells (by the neurotoxin 5,7-dihydroxytryptophan) directly affects nociception.

There is ample pharmacologic evidence that serotonin receptors in the brain can activate the hypothalamic–pituitary–adrenocortical (HPA) axis. Direct-acting serotonin agonists, serotonin-uptake inhibitors, serotonin releasers and the serotonin precursor L-5-hydroxytryptophan all increase release of adrenocorticotrophin (ACTH) and corticosterone. Serotonin-containing nerve terminals make synaptic contact with corticotrophin-releasing factor (CRF)-containing cells in the hypothalamus; and serotonin, as well as serotonin agonists, stimulate corticotropin release from the hypothalamus. Current evidence suggests that both 5-HT1A and 5-HT2 receptor subtypes are involved in the regulation of the secretion of corticotrophin-releasing factors. However, the physiology of the serotonergic regulation of the HPA axis is not well understood. Serotonin-containing neurons also appear to influence the secretion of other pituitary hormones, especially prolactin and gonadotropins.

3.8.6 Neurological Disorders and Neurodegenerative Diseases

Alterations in serotonin function have been linked to anxiety, affective, eating and sleep disorders.

In clinical trials, the 5-HT1A agonist buspirone has been found to be useful in the treatment of anxiety. Buspirone has a side-effect profile that differs from

the anxiolytic effect of benzodiazepines insofar as it has no sedating effect. 5-HT1A agonists thus offer a useful tool in the treatment of anxiety.

A role for serotonin in the origin of migraine has been supported by changes in circulating levels of serotonin and its metabolites during the cycle of migraine attacks, along with the ability of serotonin-releasing agents to induce migraine-like symptoms. An involvement of serotonin in migraine is further supported by the efficacy of serotonin receptor ligands. Sumatriptan is an agonist on 5-HT1D and 5-HT1B receptor subtypes and is effective in treating migraine pain and associated symptoms. Recently, selective 5-HT1F agonists have been proposed for the treatment of migraine, without the side-effects associated with the 5-HT1D and 5-HT1B receptor agonists. A triggering role has also been suggested for 5-HT2B receptors in the initiation of migraine, suggesting that the application of selective 5-HT2B receptor antagonists might be effective in migraine treatment. Thus, compounds that modulate 5-HT1B, 5-HT1D, 5-HT1F and 5-HT2B receptors either have or may have clinical relevance in the therapy of migraine headache.

The serotonergic system plays a significant role in the generation of depression. Functional deficiencies in serotonin and norepinephrine have been implicated in the pathophysiology of depressive syndromes; and restoration of the normal function of the 5-HT- and NE-associated signaling pathway has been the target of antidepressants. This strategy is based on the monoamine theory of depression. In this context, it is essential to mention the observation that the monoamine hypothesis of 5-HT and NE deficiencies fails to explain the whole mechanims of antidepressants; and account must be taken of the additional hypotheses, including the cytokine hypothesis of depression, the hypothalamic–pituitary–thyroid hypothesis of depression, as well as the role of brain-derived neurotrophic factor (BDNF) and cyclic AMP response elements.

Nevertheless, the monoamine hypthesis has been fruitful in conceptualizing and developing potent antidepressants. Hypoactivity of the central serotonergic system has been demonstrated in neuronal subpopulations in depressed patients, leading to the therapeutical concept of 5-HT uptake blocker application in the treatment of depression.

Selective serotonin re-uptake inhibitors (SSRI), e.g. citalopram, fluoxetine, paroxetine and sertraline, are as effective as tricyclic antidepressants. An advantage of the serotonin re-uptake inhibitors over the tricyclic antidepressants is that they induce a lower tolerance. Drugs that inhibit serotonin and norepinephrin re-uptake (SNRIs), e.g. venlafaxine, milnacipram, and duloxetine, have become a further potent class of antidepressiva. There is no evidence for major differences between the SSRIs and SNRIs in their efficacy in treating anxiety disorders. In contrast to SSRIs, which are generally ineffective in treating chronic pain, all SNRIs seem to be helpful in relieving chronic pain associated with and independent of depression.

5-HT1A agonists seem to have antidepressant properties in some animal models of depression. A noteworthy issue in this context (and somewhat contradictory to the anxiolytic effect of 5-HT receptor activation) is the finding that

some forms of phobia seem to be associated with an increase in serotonin levels, indicating that the serotinergic system is only one player in the generation of psychotic syndromes (see above).

In the treatment of psychosis, antagonists of both dopamine D2 and 5HT-2 receptors seem to be efficacious; and they reveal fewer extrapyramidal symptoms than neuroleptics that block only dopamine receptors.

A partial degeneration of serotonergic neurons occurs in some pathological states, like Alzheimer's and Chorea–Huntington's disease. In addition, in patients suffering from Alzheimer's disease, the density of 5-HT1A and 5-HT2A receptors in the cortex decreases. These deficits in serotonergic transmission might be relevant to the frequently observed depressive mood in Alzheimer's patients.

Concerning Chorea–Huntington, it has been shown that this inherited degenerative disease is coupled with a significant reduction in 5-HT1D receptors in the substantia nigra. However, the functional aspects of this reduction are essentially unknown.

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